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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference K 2675	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE99/01350	International filing date (*day/month/year*) 05 May 1999 (05.05.99)	Priority date (*day/month/year*) 05 May 1998 (05.05.98)

International Patent Classification (IPC) or national classification and IPC
C07K 16/00

Applicant
DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFTUNG DES ÖFFENTLICHEN RECHTS

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03 December 1999 (03.12.99)	21 August 2000 (21.08.2000)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE99/01350

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-15, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____.
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-21, filed with the letter of 31 July 2000 (31.07.2000),
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/10-10/10, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

See Supplemental Box

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 20 and 21

because:

☒ the said international application, or the said claims Nos. 20 and 21 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See Supplemental Box

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____ .

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE 99/01350

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

a) It was not possible for the International Preliminary Examination Authority to examine whether the protocol sequence submitted with the letter of 5 January 1999 goes beyond the content of the application as originally filed.

b) Therefore, the examination is based on the version of the protocol sequence as originally filed.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Claims 20 and 21 refer to a subject matter which, in the opinion of this authority, falls under PCT Rule 67.1(iv). Therefore, a report is not carried out as to the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-21	YES
	Claims		NO
Inventive step (IS)	Claims	1-21	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents cited in the international search report:

D1: *Journal of Immunology*, 152(11), 1994, 5368-74
D2: *Proceedings of the National Academy of Sciences of the United States of America*, 92(15), 1995, 7021-5
D3: *Journal of Immunology*, 154(9), 1995, 4576-82
D4: *Molecular Immunology*, 32(17-18), 1995, 1405-12
D5: *Journal of Molecular Biology*, 293(1), 1999, 41-56.

Document D5 was published after the filing date of the application. It describes the bivalent and tetravalent F_v antibody constructs of the invention. Both inventors are named in D5. Therefore, this T-document **can** be a **useful** aide to understanding the invention.

a) Novelty (PCT Article 33(2))

(i) Documents D1 to D4* describe (a) bispecific F_v antibody constructs with four variable domains which are combined with peptide linkers, (b) coding expression plasmids for such constructs, and (c) methods for producing such constructs, wherein coding DNAs for the peptide linkers are linked to

the coding DNAs for the four variable domains of an F_v antibody construct in such a way that the peptide linkers join the variable domains and the DNA molecule obtained therefrom is expressed in an expression plasmid.

*D1: see pages 5369-5370
*D2: see pages 7021-7022
*D3: see pages 4577-4578
*D4: see pages 1406-1408.

The peptide linkers have:

- 14 and 25 amino acids in D1 (see Figure 1, page 5370),
- 5 and 15 amino acids [Gly_4-Ser_1 and $(Gly_4$-$Ser_1)_3$] in D2 (see Figure 1, page 7022),
- 14 and 15 amino acids in D3 [$(Gly_4$-$Ser_1)_3$] (see Figure 1, page 4578), and
- 15 amino acids in D4 [$(Gly_4$-$Ser_1)_3$] (see Figure 1, page 1407).

(ii) None of documents D1 to D4 describes a multivalent F_v antibody construct joined by the peptide linkers 1, 2 and 3, in which the peptide linkers 1 and 3 have 0-10 amino acids. Consequently, the subject matter of Claim 1 can be deemed novel over the cited prior art. The same applies to the subjects of Claims 2-21 because they refer back to Claim 1.

b) Inventive step (PCT Article 33(3))

(i) The bispecific scF_v antibody molecules of D1-D4 are able to fold themselves so that a V_L domain is joined to an adjacent corresponding V_L domain. This

disadvantage is avoided in the invention due to the short peptide linkers 1 and 3 of the scF_v antibody construct. Thus, an scF_v antibody construct as per the invention can be joined to other scF_v antibody constructs, producing F_v antibody constructs with four or eight variable domains and a plurality of valences and specificities. Thus, the subject matter of Claim 1 involves an inventive step with respect to the cited prior art. The same applies to the subjects of Claims 2-13, 20 and 21 because they refer back to Claim 1.

(ii) The expression plasmids of Claims 14-19 code for bivalent F_v antibody constructs with four variable domains having two peptide linkers "GG" and one peptide linker having either 12 (("GGPGS" + 7 additional amino acids) or 27 $(G_4S_1)_4$ + 7 additional amino acids) (see document D5, page 42, right-hand column). Since two such constructs (with such a combination of peptide linkers) can fold themselves together so as to form stable tetravalent F_v antibody constructs with eight variable domains, the bivalent constructs as characterised in Claim 1 could be deemed inventive. Consequently, the subject matter of Claims 14-19 can also be deemed inventive.

c) Industrial applicability (PCT Article 33(34))

(i) The subject matter of the present Claims 1-19 appears to be industrially applicable.

(ii) The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of Claims 20 and 21 in their present form. Patentability can also depend on the wording of the

claims. The EPO, for example, does not recognise the industrial applicability of claims to the use of a compound in a medical treatment; it does, however, allow claims to the first use of a known compound in a medical treatment or to the use of such a compound in the manufacture of a drug for a new medical application.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

a) In contrast to lines 20 and 21 of page 9 of the description, Figure 6 does not indicate the complete nucleotide and protein sequences of the tetravalent F_v antibody constructs.

b) In contrast to the final sentence of Example 2 on page 10 of the description, Figure 7 does not show the nucleotide and protein sequences of the tetravalent F_v antibody construct (see the final sentence of Example 2 on page 10). A nucleotide and protein sequence is only outlined for the F_v antibody construct with four variable domains (cf. Fig. 1). There is no description of a gene that codes for a tetravalent F_v antibody construct.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

a) F_v antibody constructs with eight variable domains, that is, **tetravalent** constructs, which are also described in the application, are dimers consisting of two F_v antibody constructs with four variable domains. An F_v antibody construct such as this with eight variable domains arises if two independent (meaning that these constructs are not joined to any peptide linker) single-chain F_v antibody constructs with four variable domains are folded together (see also D5, pages 43 and 44).

The application does not describe any F_v antibody constructs with twelve or sixteen or more variable domains. In addition, the description does not explain how such an F_v antibody construct could be produced.

By using the word "*multivalent*", the claimed subject matter encompasses constructs containing more than four or eight variable domains. Consequently, Claims 1-13, 20 and 21 violate PCT Article 6.

b) Although the claims mention three peptide linkers **1, 2 and 3**, Figures 3, 4, 5, 6, 9 and 10 mention F_v antibody constructs with four variable domains containing two peptide linkers and one mean peptide linker **2 or 3**. Due to this inconsistency between the description and the claims, Claims 1-14 and Claims 21 and 22 also violate PCT Article 6. In this context, it appears that the peptide linkers should not be characterised with numbers alone.